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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,183	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-46 are pending and under consideration in this action.

Priority

With respect to claims 1-16 drawn to enhancing capacity of *impaired* bone marrow cells to promote neovascularization, applicant is granted priority to the filing date of instant application – 07/10/2003, because this embodiment does not appear to be disclosed in any of the cited priority documents. Thus, claims 1-17 are rejectable over Iwaguro et al. (Feb. 2002) for reasons given below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claim 1 and claim 17 recite the term "derived from" which confers ambiguity and indefiniteness, because the nature or number steps required to obtain a derivative are unknown.

Claim 14 recites the term, "stimulating" which does not appear to be specifically defined in the specification. There is reference to *ex vivo* stimulation of bone marrow with MCP-1, but as the term "stimulating" is subjective and open to interpretation, the metes and bounds of the claim are indefinite.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 1-46 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of hind-limb ischemia in mice, does not reasonably provide enablement for promoting angiogenesis in any tissue/organ of any animal.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman,* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The broadest claims are drawn to transfection of autologous bone marrow cells (ABM) transfected with any vector. In addition the claims are directed to enhancing collateral blood vessel formation in any site *in vivo* through transfecting ABMs and either directly administering them to any desired site or indirect administration by

injection into the blood stream. Furthermore, ABMs can be transfected with nucleic acids obtained from any source to express *any* angiogenic factor or growth factors with the expectation of enhanced angiogenesis.

Nature of the invention. The invention encompasses cell transfection and cell transplantation. All claims recite a therapeutic effect in a "patient" and transfection of cells, thus are further construed to have an intended use in gene therapy. The specification discloses that the claimed method or composition find particular use in gene therapy applications in a human patient.

Sate of the art/Unpredictability of the art. There is a substantially high level of unpredictability in the art of gene therapy. The specification does not teach *how to use* the claimed methods and composition therapeutically commensurate with the scope of the claims for the following reasons.

Gene therapy is not routinely successful. At the time the application was filed, the art of delivering transducted cells to an individual with the aim or producing therapeutic products so as to achieve a desired outcome was poorly developed and unpredictable. In a review article published in Nature in 1997, Inder Verma states, "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still not single outcome that we can point to as a success story." (*Infra*, at p. 239). Gene therapy is a highly unpredictable art with poor efficiency of delivery of the transgene to the target cells, poor transformation efficiency of target cells, unpredictable and transient expression of the transgene in target cells, etc. (See Kmiec, American Scientist, 1999, Vol. 87: 240-147; Anderson, Nature, 1998, Vol. 392: 25-30; Verma et al., Nature, 1997, Vol. 389: 239-242; reviewing the multitude

of difficulties and lack of success in gene therapy methods). Additionally, for example, vectors, including adenoviral vectors, used to deliver constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (See, Check, Erika, Feb. 13, 2003, Nature, 421: 678; citing occurrence of leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA); (see also, Juengst, ET. June 2003, BMJ, 326:1410-11; indicating that gene transfer often has multiple and unpredictable effects on cells).

The claimed methods and composition encompass a wide variety of different therapeutic genes and further encompass producing angiogenesis in virtually any region or tissue in the body. Even the most promising areas present barriers to successful gene therapy that could not be overcome with routine experimentation. For example, in the area of angiogenesis in the heart, additional mechanistic and transactional pre clinical investigations are essential, and well-designed studies are required before the great potential of adult stem cell therapy can be fully realized. (Chiu RC. Exp.Opin. Biol. Ther.; 3(2):215-25, 2003, e.g. Abstract; see entire reference). More particularly, with respect to gene therapy, the transducted cells in a human patient would need to express the angiogenic factor for a threshold period of time to promote angiogenesis (e.g. strength of expression from the promoter). Such a period of time may not necessarily be obtained, if at all, through routine experimentation with human ABMs and/or a relevant animal model.

Furthermore, in regard to the art of ABM transplantation in patients, there is unpredictability with regard to outcome. For example it is unpredictable whether patients will be able to tolerate a large number of cells. (Stamm et al. Lancet, 2003; 361:45-6, e.g. p. 46, col. 2 ;

See entire reference). Therefore, while direct transplantation of a quantity of transducted murine ABMs into syngeneic animals may show some success, this would not necessarily translate into routine success in a human or related animal model. Moreover, "All gene therapy designed to potentiate local angiogenesis carries the theoretical risk that pathological angiogenesis at a remote site could be stimulated, ie, ocular angiogenesis or tumor angiogenesis." (Folkman, J. Circulation; 87:1108-1110 (1998); see p. 1108, col. 2; See above notes). In addition, ABMs transfected with adenoviral vectors would at least to some extent express viral proteins, which may induce a deleterious immune response in a human patient. Even current understanding of myogenic stem cell transplantation, including utilizing gene therapy, is that "With respect to the ultimate clinical utility of myocyte and myogenic stem cell transplantation, it is important to recognize that we are still very early in the game." (Dowell et al. Cardio. Res., 58:336-350 (2003), at p. 347, col. 2; see above notes). Therefore there are clearly obstacles to routine practice of the claimed invention and such obstacles should not be construed as safety concerns, but rather, as obstacles that obviate the invention's use without undue experimentation. The instant specification does not adequately teach one skilled in the art *how to use* the claimed invention for *in vivo* therapy in a human patient, where transducted ABMs are administered at any location in the body where angiogenesis is deemed needed.

Amount of guidance provided. There is some generic guidance provided, but no significant guidance is provided with respect to gene therapy or transfection of ABMs and treatment of a human patient.

Number of working examples. A single is example provided that encompasses direct administration of murine bone marrow cells, which are transfected with adenovirus encoding

HIF-1α/VP16, directly into an ischemic limb of syngeneic mice. This result is not necessarily predictive of success in *any* organ/tissue, using *direct* or *indirect* administration and in *any* animal or humans (see notes above under State of the Art).

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles and obstacles to successful practicing of the invention, the level of unpredictability in the art and limited relevance of working examples as related to the obstacles presented, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

Written Description

3. Claims 1-9, 11-12, 14-16, 18-28, 33-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter, transfection with any angiogenic ctyokine, growth factor or angiogenesis-promoting factor, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to transfecting ABMs with a genus of growth or angiogenic factors for effectuating angiogenesis in any animal subject. The specification provides a single example of HIF-1, a hypoxia-related promoter of VEGF expression. This single is not necessary predictive of all angiogenic factors. The disclosure does provide a list of additional factors (e.g. FGF-1, FGF-2, FGF-4, FGF-5, NOS and PR39). However, the claims encompass any

angiogenic factor in treatment of any animal and in any tissue/organ, thus the disclosure is not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all angiogenic factors that can be used to effectuate angiogenesis based on the teachings in the specification.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

Given the enormous breadth of the growth and angiogenic factors encompassed by the rejected claims, and given the limited description from the instant specification of such factors, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of growth and angigoenic factors. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 17-28 and 31-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-18, 9, 24, 25, 27, 30-31, of copending Application No. 09/868,411 ('411 application; hereinafter "reference claim(s)").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other as discussed below:

The claims in instant and reference application, while not identically written, are not patentably distinct. For example, instant claim 17 recites, "growing [ABMs] under suitable conditions in a container for a period of time sufficient to promote production by the bone marrow of early attaching cells". Similarly, instant base claim 39 recites, "A therapeutic composition comprising early attaching cells" when referring to the composition claimed. In addition instant base claim 18 is drawn to culturing and processing ABMs, as well as involving growing and filtering cells (dependant claim 25). Instant claims are directed to a method of enhancing collateral blood vessel formation by transfecting ABMs with genes for angiogenic factors, and subsequently administering the cells to a desired site. Additionally, plasmid or adenoviral vectors are used to transfect ABMs.

Reference claims 1, 10 and 11 are directed to a method of enhancing collateral blood vessel formation, which comprises transfection of ABMs with angiogenic genes and administering the cells to a desired site. Thus, the skilled artisan would observe that reference claims 1, 10 and 11 are drawn to ABM transfection with any agent enhancing collateral blood vessel formation.

Instant claims 20-22 and 33 are drawn to directly injecting transfected ABMs into the heart, leg, artery, ischemic site or blood stream. Reference claims 3-6, 19-20 are recite that ABMs are "injected", "injected intramyocardially", via catheter (e.g. intracoronary) or into the limb intramuscularly.

Instant claims 35-38 are drawn to additional embodiments where enhanced collateral blood vessel formation promotes development of newly implanted myocardial cells, electrical conductivity, myocardial function and treats left or right ventricular conditions. Similarly, reference claims 19, 29, 36, 46, 53, 63, 70 and 80 are drawn to application of ABMs to promote development of newly implanted myocardial cells (19 and 29), electrical conductivity (36 and 46), myocardial function (53 and 63) and ventricular conditions (70 and 80).

In addition instant claims 39-46 are drawn to compositions comprising early attaching cells (i.e. cultured ABMs) transfected with angiogenic factors (i.e. genes), with additional embodiments where cells are exposed to hypoxia, and further comprise anticoagulants. Reference claims 80, 91, 93, and 96 are drawn to nearly indistinguishable subject matter.

In sum, the reference claims anticipate, thus necessarily make obvious the instant claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-7 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwaguro et al. (Circulation; 105(6):732-38 (Feb. 12, 2002); see whole document.)

Iwaguro et al. teach a method of enhancing vascular regeneration using heterologous bone marrow-derived progenitor cells (EPCs) in nude mice. The reference teaches that angiogenesis can be *impaired* due to certain disorders, such as hypercholesterolemia, aging or diabetes. (e.g. p. 732, col. 2). Therefore, the reference is suggestive that treatment in such groups, which would necessarily require EPCs be expanded from such groups for the purposes of treatment. In other words, the EPCs harvested would be *impaired* EPCs by definition. Furthermore, the progenitor cells are expanded *ex vivo* prior to transfection (e.g. p. 733, col. 1, ¶ 1), where the cells are grown until early attaching cells are present and nonadherent cells are washed away (Id.). The cells are grown up to 7 days prior to transfection (Id.), with an

adenovirus encoding murine Vascular Endothelial Growth Factor (VEGF). (e.g. p. 733, col. 1, ¶ 2). Subsequently, the cells cultured and transplanted into nude mice with hind limb ischemia, wherein neovascularization and blood flow recovery were both improved. (e.g. Abstract, p. 733, col. 2, ¶ 2; p. 735, col. 1 bridging to col. 2).

Iwaguro et al. do not teach use of autologous bone marrow-derived cells, but instead teach that heterologous cells are used in nude mice. However, it would be evident to one of ordinary skill in the art, that such a model system could be extrapolated to autologous cells from a source w/ impaired ABMs, similarly manipulated in *ex vivo* expansion and transfection with an adenoviral vector. Indeed, Iwaguro et al. expressly indicate that the results can be extrapolated to autologous transplantation. (e.g. p. 737, col. 1, ¶ 3). The motivation to do so would be to promote EPC mobilization (Id.), which would be more likely where cells are not attacked by the host's immune system.

Therefore, it would have been obvious at the time of invention for one to extrapolate the system taught by Iwaguro et al. to autologous bone marrow-derived progenitor cells, in *ex vivo* expansion and transfection with an angiogenic factor. Given the skill in the art at the time of invention, one would have had a reasonable expectation of success in doing so.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER